

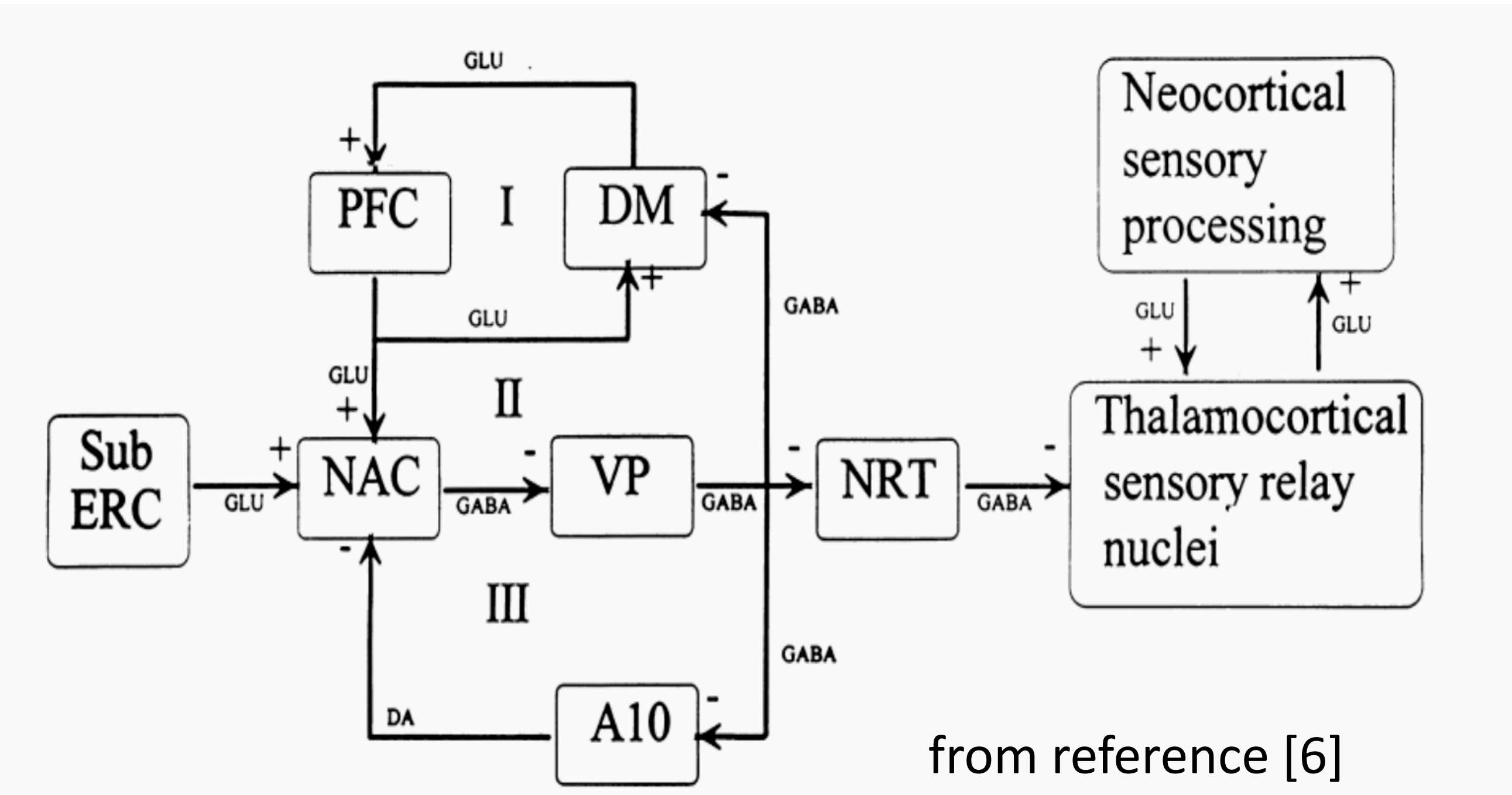
Stress, schizophrenia, and latent inhibition: what's the connection?

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Abstract

Latent inhibition is an attentional phenomenon under which conditioning to a given stimulus is retarded upon repeated stimulus presentation [1]. Interestingly, latent inhibition is impaired in individuals with schizophrenia as compared with individuals without schizophrenia. The close homolog to L1 (CHL1) gene has been linked to the genetic predisposition to f schizophrenia [2]. Mutations in the CHL1 gene are known to affect brain development, particularly neuronal migration and development of neuronal connections, as well as cellular signaling pathways [3,4,5]. In this experiment CHL1 knockout (KO) and wild type (WT) mice received six weeks of chronic mild stress (CMS). We hypothesized that CMS might bring about the onset of schizophrenia-like behaviors in the KO mice. The mice were tested behaviorally in a latent inhibition paradigm, then sacrificed for histology. c-fos immunohistochemistry staining was performed to assess neuronal activation; c-fos is a gene encoding a transcription factor which is transcribed immediately following neuronal activity (immediate early gene), making it a useful tool to observe differences in activation in the context of specific behaviors. Neural activation in several brain regions involved in latent inhibition was analyzed and results were compared between the different genotypes and behavioral groups. Brain regions were selected based upon the known circuitry of the latent inhibition network, a diagram of which can be seen below.



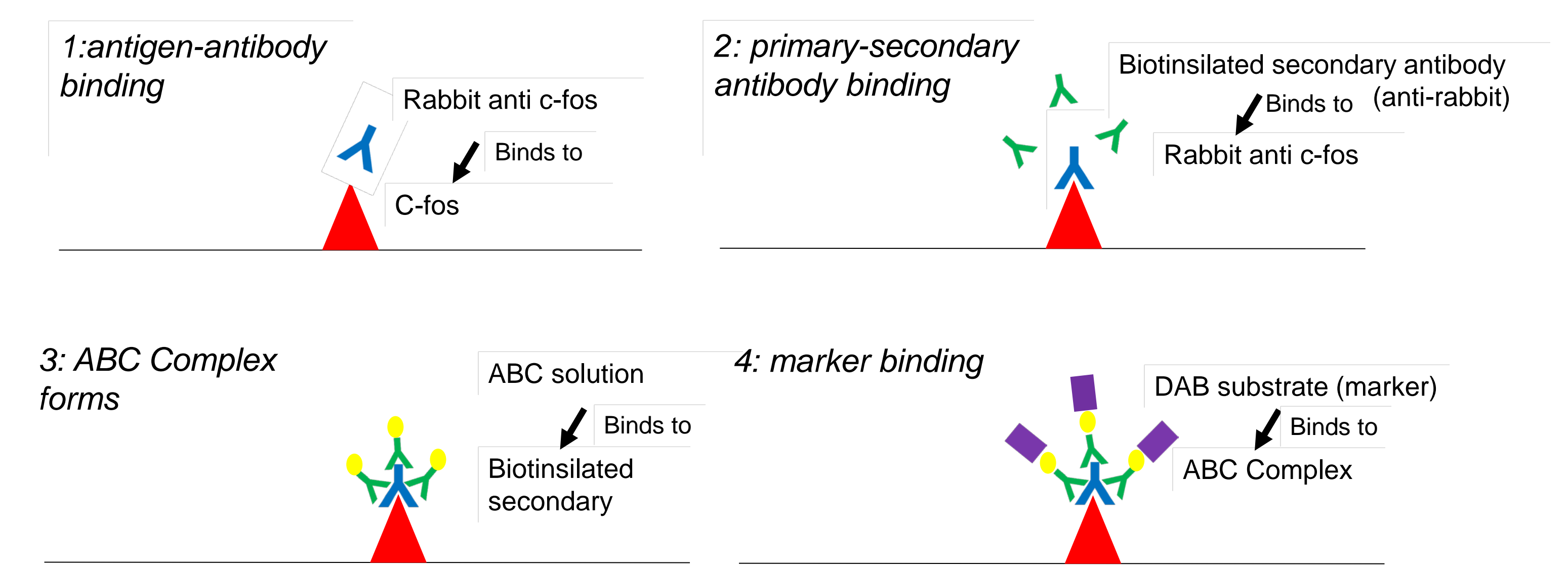
References

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Methods

Subjects & prep: 50 μ m free floating brain sections were collected from 8 mice using a vibratome. 4 mice, 2 WT, and 2 KO were exposed to chronic mild stress before testing, while 4 mice, 2 WT, and 2 KO were tested without prior stress conditioning.

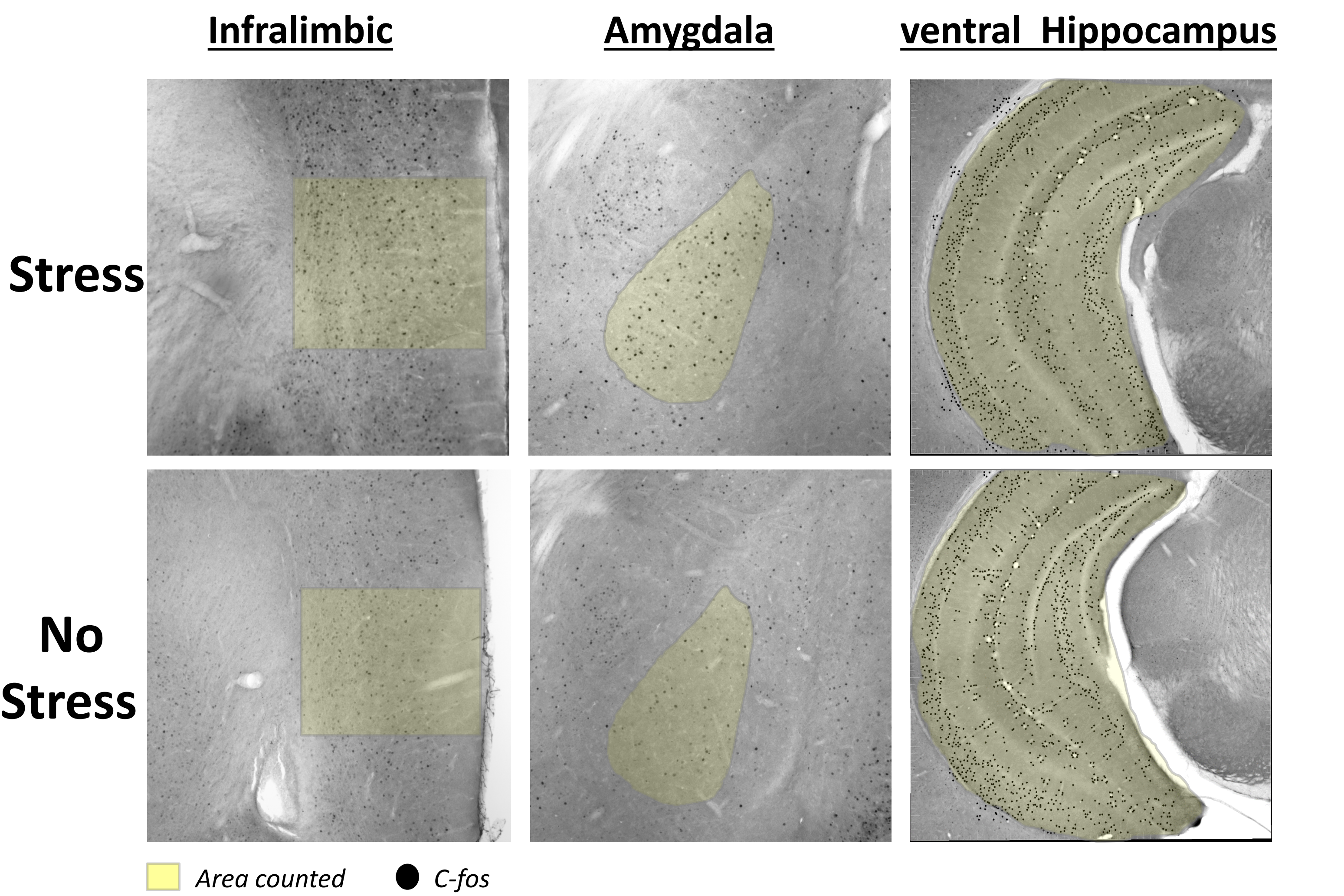
Immunohistochemistry (ABC) Method: Staining was performed using a rabbit anti c-fos (Calbiochem) primary antibody, vector biotinylated secondary antibody, vector ABC solution, and vector DAB substrate kit. The process shown in detail in the figures below.



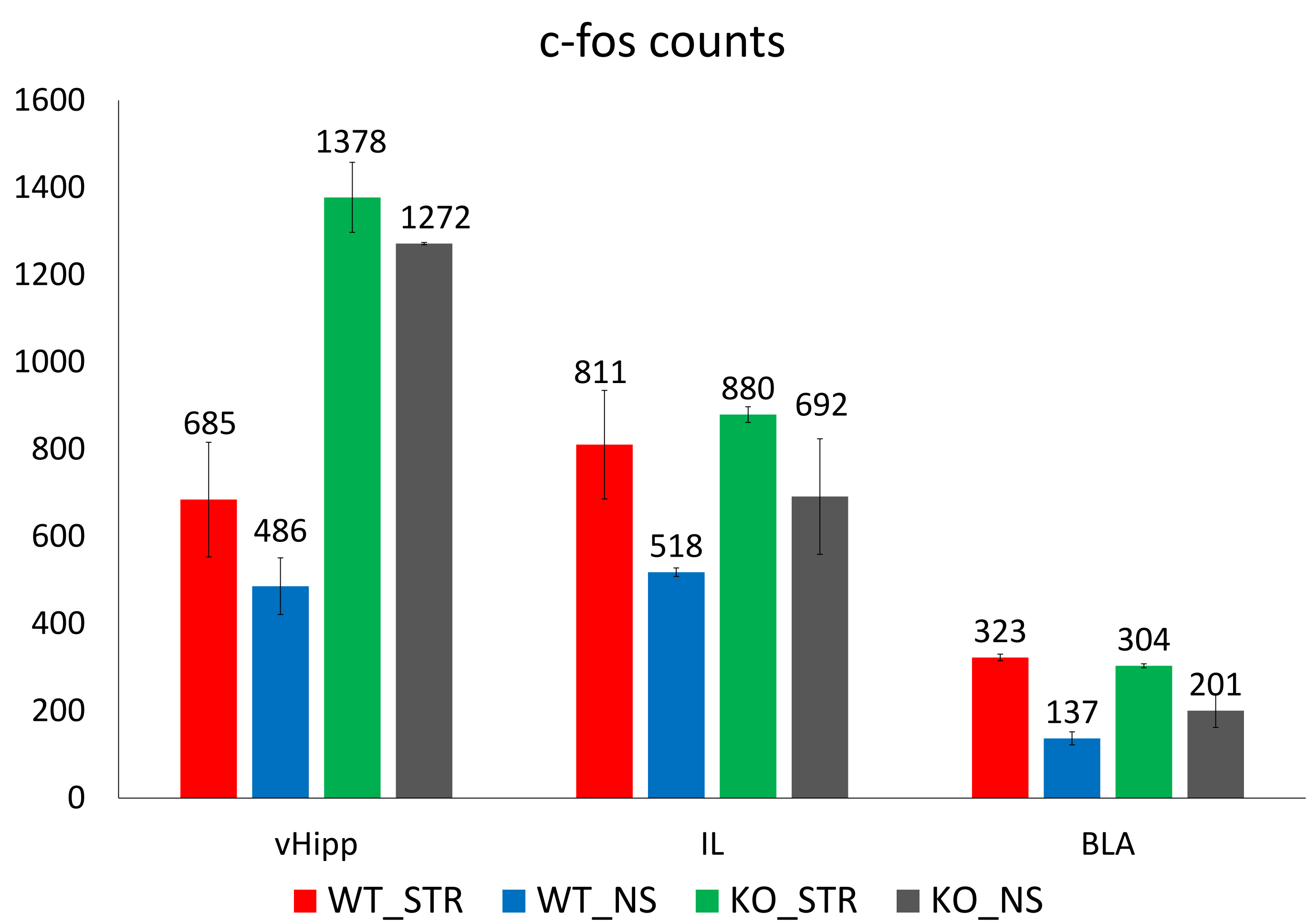
Microscopy: Pictures from 3 brain regions, the Infralimbic cortex, the basal lateral amygdala, and the Ventral Hippocampus were taken. approximate bregmas observed were 1.70, -1.70, and -3.24 respectively.

Counting: Imaris cell counting software was used to perform cell counts.

Histology



Results



- Mice exposed to chronic mild stress showed increased neuronal activation of amygdala and infralimbic cortex.
- KO mice showed significantly more neural activation of ventral hippocampus than their WT littermate controls.

Conclusions

- Our findings indicate that irrespective of genotype, mice exposed to chronic mild stress showed increased neural activation in all brain areas examined compared to mice not exposed to stress, suggesting that stress may play a role in our ability to classify a stimulus as inconsequential.
- Our results also indicate that KO mice showed increased neural activation of the ventral hippocampus, suggesting that ventral hippocampus may play a role in the development of schizophrenia for individuals with mutations in the CHL1 gene.

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